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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,523	08/17/2005	Barton Haynes	1579-968	7798

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,523	HAYNES ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *18-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 01 December 2008. Claims 21 and 22 have been added. Claims 1-22 are pending. Claims 18-22 are drawn to a nonelected subject matter and hence are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 1-17 are currently examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-12 under 35 U.S.C. §103(a) as being obvious over Ross *et al.* (2001, hereinafter "Ross") in view of Shearer *et al.* (1995, hereinafter "Shearer"), as evidenced by Rizzuto *et al.* (1998), is maintained.

The instant claims are directed to a fusion protein comprising: (i) an IgG Fc component, (ii) an HIV envelope (Env) component, and (iii) a C3d component; and a composition comprising the fusion protein.

Ross discloses a DNA vaccine expressing a fusion protein of murine C3d fused to the C-terminus of HIV Env gp120 (recited in claim 9) that is administered into mice with gold beads as a carrier (recited in claims 11 and 12). See pages 2-3. Ross further discloses that one consequence of complement activation is the covalent attachment of the C3d to antigen. C3d in turn binds to CD21 on B lymphocytes (recited in claim 8),

which ultimately amplifies B cell activation and antibody production. See page 2, middle full paragraph.

Ross does not specifically describe a fusion protein of HIV Env gp120 and human C3d. However, Ross discloses that in the human immune system, C3d is one of the final degradation products of the third complement protein, C3. See page 2, middle full paragraph. Thus, Ross provides the motivation to make a fusion protein of HIV Env gp120 and human C3d (recited in claim 7) when the host to be administered the immunogen is changed from mice to human. As evidenced by Rizzuto *et al.* (1998), the gp120 protein comprises the V3 domain towards its C-terminus and includes a B cell neutralizing antibody epitope.

Ross does not disclose the IgG Fc component of the claimed fusion protein. Shearer discloses a fusion protein by fusing the gp120 binding domain of CD4 to the Fc portion of the human IgG1 (recited in claim 6) heavy chain. See Abstract and page 281. This chimeric protein retains certain properties of human IgG, including a prolonged half-life in serum and Fc receptor binding. See page 281, the sentence connecting the left and right column. Furthermore, Shearer discloses linkers composed of two repeats of four glycines and a serine were fused at the junctions of Env and C3d (recited in claim 5). See page 3, lines 7-8.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Shearer's human IgG Fc component to either the N-terminus (recited in claims 1-4) or the C-terminus of Ross' fusion protein of gp120-C3d for the purpose of increasing the serum half-life of gp120-C3d. The skilled artisan

would have a reasonable expectation of success because Shearer suggests that human IgG Fc prolongs the serum half-life of the gp120 binding domain of CD4. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that nothing in Ross and/or Shearer would have suggested a fusion protein comprising IgG Fc, gp120 and C3d, nor would the references have provided any basis for a reasonable expectation of generating a successful product. Applicant dismissed Examiner's rationale for combining Ross and Shearer by arguing that these assertions do not constitute the type of reasoning required to support the contention that the combination of references would have led an artisan to the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Ross provides the motivation to make a fusion protein of HIV Env gp120 and human C3d (recited in claim 7) because Ross discloses that fusing three copies of murine C3d to the carboxyl terminus of the HIV Env gp120 subunit induces higher antibody responses to Env and a

faster onset of avidity maturation than does the wild type gp120 (page 2, third paragraph). In the human immune system, C3d is one of the final degradation products of the third complement protein, C3. One consequence of complement activation is the covalent attachment of the C3d to antigen. C3d in turn binds to CD21 on B lymphocytes, a molecule with B cell stimulatory functions that amplify B lymphocyte activation. Thus, it would be obvious to one skilled in the art to replace the murine C3d with human C3d to induce higher antibody responses to HIV Env gp120 in a human body.

Furthermore, Shearer provides the motivation to fuse one more protein component, IgG Fc, to Ross's fusion protein of gp120-C3d because Shearer discloses that fusing IgG Fc to an antigen, gp120-binding domain of the CD4 protein, prolongs the fusion protein's half-life in serum and Fc receptor binding (page 281, see the sentence bridging the two columns). Longer serum half-life means that the antigenic protein remains in the human body longer and induces more antibody responses. Examiner appreciates Applicant's summary of Shearer's teaching of mother-infant HIV transmission. However, this extraneous fact is not relevant to the claimed invention and thus not germane to the rejection at issue. On the other hand, Applicant does not present any showing or scientific reasoning to support his contention that Examiner's rationale pertaining to the longer serum life and Fc receptor binding does not provide any basis for a reasonable expectation of success. Applicant has not explained why these rationales pertaining to extended serum half-life and Fc receptor binding, which in turn leads to higher antibody response, do not constitute the type of reasoning required

to support the combination of references leading to the claimed invention. In other words, Applicant has not presented any evidence proving otherwise than the expected advantage of higher antibody response.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant also argues that the alleged motivations are not mentioned in the cited references. This is not the standard. The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to

explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

The rejection of claims 13, 14, 16 and 17 under 35 U.S.C. §103(a) as being obvious over Ross *et al.* (2001, hereinafter "Ross") in view of Shearer *et al.* (1995, hereinafter "Shearer") and DeVico *et al.* (US 5,518,723, hereinafter "DeVico"), as evidenced by Rizzuto *et al.* (1998), is maintained.

The instant claims are directed to a complex comprising a fusion protein comprising: (i) an IgG Fc component, (ii) an activated ligand-bound HIV envelope (Env) component, and (iii) a C3d component..

The disclosure of Ross and Shearer is set forth above. Neither reference discloses a ligand-bound HIV Env.

DeVico teaches an immunogen, called gp120-CD4 complex, which is the recombinant HIV envelope protein gpl20 chemically crosslinked to a soluble CD4 ligand (column 1, lines 7-12). DeVico further teaches that the gp120-CD4 immunogen exposes cryptic epitopes on gp120 that induces neutralizing antibodies to gp120 (column 7, lines 37-47). Still further, DeVico teaches that the CD4-complexed gp120 appears to undergo a conformational change that present an array of epitopes (recited in claim 13) that were hidden on the uncomplexed glycoprotein. Covalently bonded CD4-gp120 complexes are useful for raising neutralizing antibodies against various

isolates of HIV-1 and against HIV-2 (column 1, lines 57-67; column 2, lines 1-2). As evidenced by Rizzuto *et al.*, CD4 binding to HIV gp120 can induce (up-regulate) the CCR5 binding site on gp120, facilitating HIV fusion to a host cell via CCR5 co-receptor (whole document, particularly Abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Shearer's human IgG Fc component to either the N-terminus (recited in claims 1-4) or the C-terminus of Ross' fusion protein of gp120-C3d for the purpose of increasing the serum half-life of gp120-C3d, and to further modify the fusion protein by crosslinking a CD4 molecule to the middle component, HIV Env gp120, so as to raise neutralizing antibodies. The skilled artisan would have a reasonable expectation of success because Shearer suggests that human IgG Fc prolongs the serum half-life of the protein that the IgG Fc is fused to and because DeVico teaches that CD4-complexed gp120 raises non-strain-specific neutralizing antibodies against both HIV-1 and HIV-2. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that nothing in DeVico would have motivated an artisan to combine the teachings thereof with those of Ross and Shearer. However, as set forth in the precious Office Action, DeVico provides the motivation to covalently bind CD4 to the gp120 in the fusion protein complex of IgGFc-gp120-C3d as suggested by Ross and Shearer because DeVico discloses that the covalently bonded CD4-gp120 complexes are

useful for raising neutralizing antibodies against various isolates of HIV-1 and against HIV-2. Each modification to Ross' fusion protein of gp120-C3d is for the purpose of raising higher titers of antibody response, as expressly taught by Shearer and DeVico. Therefore, the combination of references in the instant case is properly motivated.

Applicant's assertion of no expectation of success in the combination lacks reasoning and/or evidentiary basis. Applicant has not provided any showing to support the contention that nothing in the combination provided basis for expecting success. Applicant has never submitted the scientific reasoning for inoperability of the product according to the way the Examiner combines the prior art teachings. Applicant has never shown why one skilled in the art would not raise higher antibody response if Ross's gp120-C3d fusion protein was modified to the IgG Fc-gp120-C3d fusion, as motivated by Shearer, to achieve a longer serum half-life and better Fc receptor binding (which means longer stimulation of the immune response), and if the fusion protein was further modified to the IgG Fc-gp120=CD4-C3d fusion protein, as motivated by DeVico, to increase the spectrum of immune responses by raising neutralizing antibodies against various isolates of HIV-1 and against HIV-2.

The rejection of claims 13-15 under 35 U.S.C. §103(a) as being unpatentable over Ross *et al.* (2001, hereinafter "Ross") in view of Shearer *et al.* (1995, hereinafter "Shearer") and Wyatt (1995, hereinafter "Wyatt"), as evidenced by Rizzuto *et al.* (1998), is maintained.

The instant claims are directed to a complex comprising a fusion protein comprising: (i) an IgG Fc component, (ii) an HIV envelope (Env) component bound to an antibody, and (iii) a C3d component.

The disclosure of Ross and Shearer is set forth above. Neither reference discloses a ligand-bound HIV Env.

Wyatt discloses a complex comprising HIV gp120 bound to a monoclonal antibody (recited in claim 15), which is shown as the wild-type gp120-17b and wild-type gp120-48d control in precipitation in Figure 2A and B (see also page 5726, right column, last paragraph) and as the wild-type gp120-A32 control in Figure 4 and Figure 5 (see also page 5728, right column). Upon the binding of soluble CD4, HIV gp120 experiences conformational changes and up-regulates (exposes) the conserved, discontinuous epitope on the HIV gp120. The binding of the A32 antibody to the wild type envelope glycoprotein gp120 activates the gp120 so that mAbs 17b and 48d recognize and bind to the exposed conformational epitopes and form gp120/mAb A32/17b or gp120/mAb A32/48d complex. See page 5728, right column and Figure 5.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add Shearer's human IgG Fc component to either the N-terminus (recited in claims 1-4) or the C-terminus of Ross' fusion protein of gp120-C3d for the purpose of increasing the serum half-life of gp120-C3d, and to further modify the fusion protein by binding an antibody to the middle component, HIV Env gp120, so as to raise more neutralizing antibodies, per the suggestion of Wyatt. The skilled artisan would have a reasonable expectation of success because Shearer

suggests that human IgG Fc prolongs the serum half-life of the protein that the IgG Fc is fused to and because Wyatt teaches that mAb-complexed gp120 exposes more epitopes for other neutralizing antibodies. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that nothing in Wyatt would have motivated an artisan to combine the teachings thereof with those of Ross and Shearer. However, as set forth in the precious Office Action, Wyatt provides the motivation to bind monoclonal antibody (mAb) to the gp120 in the fusion protein complex of IgG Fc-gp120-C3d as suggested by Ross and Shearer because Wyatt discloses that mAb-complexed gp120 exposes more epitopes for other neutralizing antibodies. Each modification to Ross' fusion protein of gp120-C3d is for the purpose of raising higher titers of antibody response, as expressly taught by Shearer and Wyatt. Therefore, the combination of references in the instant case properly establishes a *prima facie* case of obviousness.

A suggestion or motivation to combine references is an appropriate method for determining obviousness, however it is just one of a number of valid rationales for doing so. The Court in KSR identified several exemplary rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in Graham. KSR, 550 U.S. at ___, 82 USPQ2d at 1395-97. See MPEP § 2141 and § 2143.

The expectation of the advantage of raising higher titers of antibody response has been presented as the rationale for combining the cited references. However, Examiner's rationales for the combination of cited prior art were dismissed by the Applicant as "comments only on the combination of Shearer and Ross and, separately, the combination of Ross and Wyatt." Applicant does not support the contention of no expectation of success with any scientific reasoning or evidence such as an immunogenic result that is different from the expected advantage of higher antibody response. If a *prima facie* case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the prima facie case. See, e.g., *In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990). Rebuttal evidence and arguments can be presented in the specification, *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995), by counsel, *In re Chu*, 66 F.3d 292, 299, 36 USPQ2d 1089, 1094-95 (Fed. Cir. 1995), or by way of an affidavit or declaration under 37 CFR 1.132, e.g., *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687; *In re Piasecki*, 745 F.2d 1468, 1474, 223 USPQ 785, 789-90 (Fed. Cir. 1984). However, arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., *In re Huang*, 100 F.3d 135, 139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); I*n re De Blauwe*, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984).

For above reasons, all three grounds of rejection under 35 U.S.C. 103 are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,

/L. H./
Examiner, Art Unit 1648

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

11 February 2009